Mouse models of inflammatory bowel disease

Fergus R Byrne[1] & Joanne L Viney[2]*

Addresses
[1]Amgen Inc
Department of Inflammation Research
One Amgen Center Drive
Thousand Oaks
CA 91320
USA

[2]Amgen Inc
Department of Inflammation Research
1201 Amgen Court West
Seattle
WA 98119
USA
Email: vineyj@amgen.com

*To whom correspondence should be addressed

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The past decade has seen an abundance of new mouse models that mimic the human inflammatory bowel diseases (IBDs), Crohn's disease and ulcerative colitis. These mouse models of IBD have provided great insight into the potential mechanisms that drive homeostatic dysregulation in the intestine, which manifests as mucosal inflammation. Within this review, the different animal models that have been employed to gain a greater understanding of the pathogenesis of IBD are discussed and some of the new biological drugs that have emerged as potential therapeutics as a result of these mouse modeling studies are reviewed.

Keywords Crohn's disease, IBD, inflammation, inflammatory bowel disease, mouse, ulcerative colitis

Abbreviations

CD	Crohn's disease
DSS	Dextran sodium sulfate
IBD	Inflammatory bowel disease
IL	Interleukin
IFN	Interferon
TCR	T-cell receptor
TGF	Transforming growth factor
TNF	Tumor necrosis factor
UC	Ulcerative colitis

Introduction

The term inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and ulcerative colitis (UC), and is distinct from irritable bowel syndrome (IBS). Although IBD and IBS often have similar outward disease symptoms of intestinal upset, IBD is clearly an inflammatory disease, whereas IBS results from dysregulated enervation of the gastrointestinal tract. CD and UC each have a prevalence of ~ 600,000 in the US, with a similar incidence of ~ 25,000 reported new cases of each condition per year. The gender distribution of each disease is similar and onset can occur at any time in life, although there are peaks of presentation between the ages of teens to 20s and 60s to 70s [1•].

The primary pathology of these diseases is one of intestinal inflammation with clinical symptoms of nausea and diarrhea and frequent extra-intestinal manifestations ranging from osteopenia to uveitis, and also fistulizing disease in CD [2-4]. The symptoms of both CD and UC vary in severity over time and between individuals. CD can result in inflammation anywhere along the length of the gastrointestinal tract, whereas UC is confined to the colon.

Preclinical and clinical data suggest that the underlying pathogenesis of IBD is a dysregulated immune response to non-pathogenic commensal luminal antigens [5,6], largely comprising the intestinal microflora (a complex and dynamic living system which is poorly characterized and understood and may, in fact, be considered a self-antigen) [7,8]. While there is no clear etiology for IBD, recent research has demonstrated a complex interplay between polygenetic predisposition and environmental exposure. Traditional medical therapy has focused mainly on broad-spectrum immunosuppressive drugs such as corticosteroids and sulfasalazine-based compounds. Total colectomy is curative for UC but removal of the affected area in CD can result in re-occurrence of the disease in adjacent tissue (pouchitis).

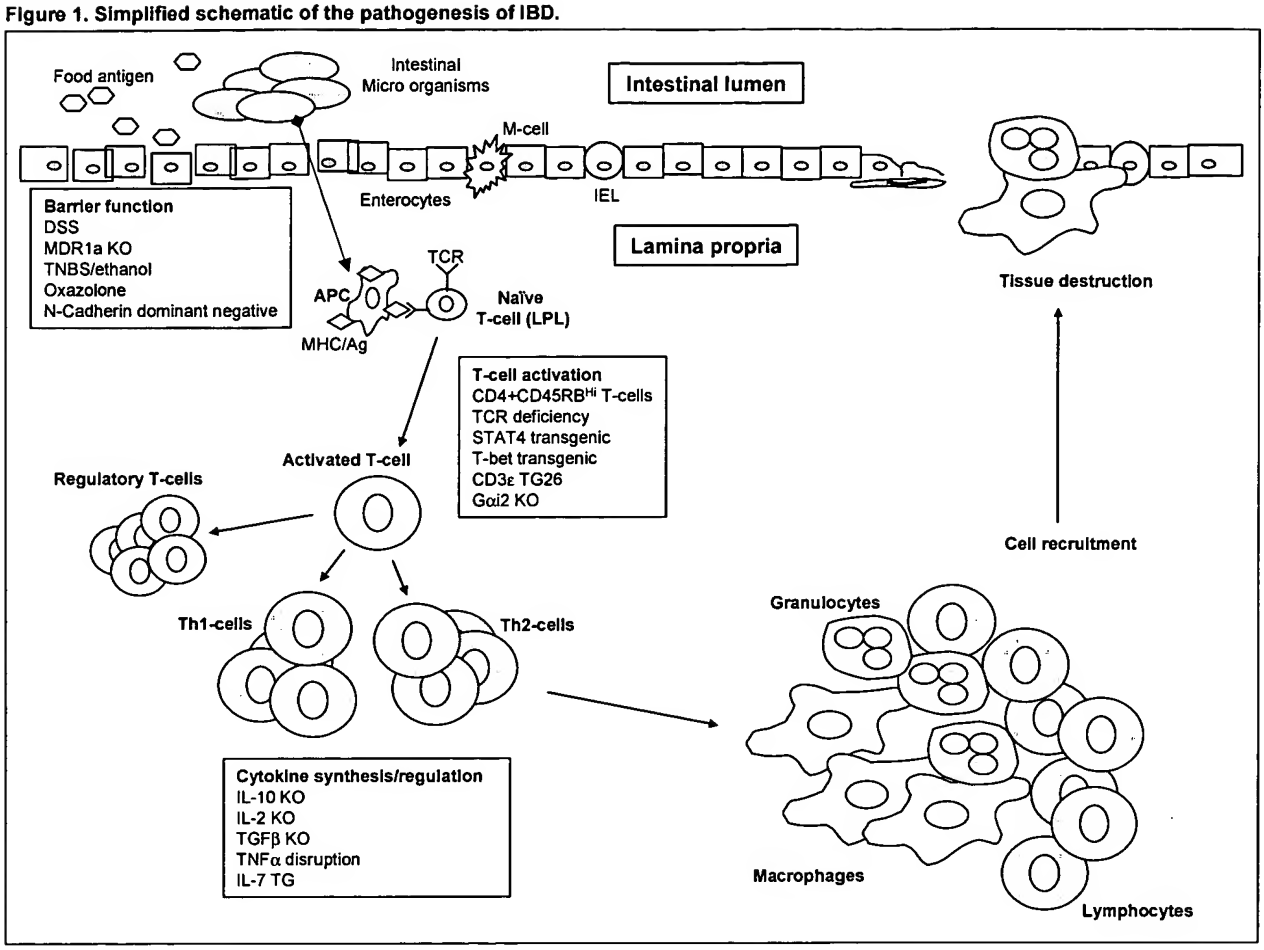
Recent advances in research have identified key pathways and molecules important in the pathogenesis of IBD: CD appears to be a Th1-like autoimmune disease, as evidenced by increased levels of tumor necrosis factor-α (TNFα) and interferon-γ (IFNγ), whereas UC is non-Th1-like [9-11]. UC has been postulated to be a Th2-like autoimmune disease but there is no strong evidence for a Th2-like phenotype. Pharmacologically, TNFα antagonists are the best clinically validated modern drugs for the treatment of both CD and UC [12••]; however, many novel potential therapeutics are under investigation and there is now a continuous cycle of preclinical research being conducted that is leading to clinical trials, the results from which will feed further basic research.

Animal models of IBD

In contrast to a mere decade ago, there now exist a variety of animal models of IBD. The different models recapitulate different facets of what is a complex and multi-factorial disease, underscoring the fact that many different pathways can converge on a final, common, broadly similar but still heterogenous and variable phenotype (Figure 1).

For many years, the spontaneous terminal ileitis observed in the cotton-top tamarin primate was the only useful animal model system for IBD, but limited numbers of animals and a lack of species-specific experimental reagents, particularly for novel protein therapeutics, precluded its routine use [13-15]. Mouse models for IBD are by far the best characterized models and thus are perceived as the most useful. Research using mouse models has revealed that

Figure 1. Simplified schematic of the pathogenesis of IBD.



The single-cell epithelial layer separates the luminal contents of the gut from the lamina propria tissue that comprises the bulk of the intestine. The layer comprises mainly enterocytes but also contains specialized cells that are capable of sampling and presenting antigens to the immune cells in the tissue, including microfold cells (M-cells). This process usually results in a steady state of continuous presentation of food and microbiological antigens to the mucosal immune system and a low level of self-limiting inflammation. In this scenario, the regulatory T-cell population is likely to be able to contain the proliferation and effector functions of differentiated Th1- or Th2-cells. If the strength and persistence of this immune response is increased by any of the perturbations described herein then uncontrolled T-cell activation, inflammation, tissue destruction and the clinical symptoms of IBD will ensue.
APC Antigen-presenting cell, **DSS** dextran sodium sulfate, **IEL** intra-epithelial lymphocyte, **IL** interleukin, **KO** knockout, **LPL** lamina propria lymphocyte, **MDR1a** multiple drug resistance 1a, **MHC/Ag** major histocompatibility complex antigen, **TCR** T-cell receptor, **TGF** transforming growth factor, **TNBS** trinitrobenzene sulfonic acid, **TNF** tumor necrosis factor.

T-cells, specifically the CD4+ subset, are key drivers of IBD, although the ultimate inflammatory response involves mixed cellular infiltration of the gut tissue. CD8+ T-cells are likely to have an accessory role in the disease, but there is no confirmed role for B-cells in the models of the disease. The currently available murine experimental systems for studying IBD pathogenesis can be broadly categorized according to where the primary disruption in healthy intestinal homeostasis occurs (Figure 1).

Disruption of barrier function

Dextran sodium sulfate-induced colitis

The IBD model induced by the *ad libitum* administration of dextran sodium sulfate (DSS) in water is popular because of its speed and ease of use, and is extremely robust and reproducible. The model manifests as colonic disease, with the most severe disease occurring in the distal colon in which a mixed cell inflammatory infiltrate comprising lymphocytes, macrophages and granulocytes develops [16,17]. Importantly, reduced consumption of DSS in water due to disease is not a factor in mitigating the phenotype [18•]. IBD can be induced in mice or rats using this method. DSS-induced disease has been reported to occur in gnotobiotic and immunodeficient mice, bringing into question its clinical relevance [19,20]. However, it appears that the combination of commensal intestinal bacteria and T-cells may play an additive role in driving an enhanced inflammatory response, since antibiotics or probiotic bacteria can modulate active disease and the colitis is attenuated by intrarectal cyclosporin [21-23]. The DSS model has proved particularly useful for testing epithelial repair agents, and in addition has also been used for testing

biologicals and cytokine inhibitors of TNFα, interleukin (IL)-18 and IL-1 [24-27]. Cycling the DSS administration with water alone is an interesting variation of the method and may provide a better model of the chronicity of human disease.

Trinitrobenzene sulfonic acid- and oxazolone-induced colitis

IBD models induced by intrarectal administration of trinitrobenzene sulfonic acid (TNBS) in ethanol, or oxazolone, with or without prior sensitization, display a similar profile to a delayed-type hypersensitivity reaction in the gut. TNBS-induced disease is primarily colonic [28]: the ethanol solvent permeabilizes the epithelium near the administration site and the TNBS acts as a sensitizing hapten. The disease is modulated as expected in TNFα knockout and transgenic mice, indicating clinical relevance [29•]. The model is robust, and has proven effective in many studies with cytokine antagonism [30-33]. Preclinical findings with IL-12 antagonism [34-36] have led to clinical trials being conducted in CD patients with antibodies to human IL-12 p40, and efficacy in phase II clinical trials has been reported [37]. Oxazolone-induced disease is considered to be more Th2-like and thus more UC-like, due to IL-4 and IL-13, but not IL-12 antagonism being effective in treatment [38,39]. Other traditional anti-inflammatory drugs are also effective in treating oxazolone-induced disease [40].

P-glycoprotein deficiency and N-cadherin transgenic colitis

Multiple drug resistance 1a (*mdr1a*)-knockout mice spontaneously develop colonic disease and typhlitis, with variable penetrance and synchronicity depending on the animal intestinal microflora. The absence of the *mdr1a* gene product P-glycoprotein in the epithelial cells (rather than the lymphocytes) confers susceptibility to disease, resulting in a disruption of barrier function but without the loss of the actual epithelial barrier [41]. Treatment with broad-spectrum antibiotics eliminates disease, confirming the clinical relevance of this model, although comprehensive benchmarking studies with drugs have not been conducted [42]. Less well characterized, but nonetheless interesting, is the barrier dysfunction that occurs in the dominant negative N-cadherin mouse model, whereby gut epithelial expression of dominant negative N-cadherin interferes with healthy E-cadherin homotypic interactions, resulting in the physical breakdown of the epithelial barrier and the occurrence of patchy IBD-like disease [43].

These barrier function disruption models clearly demonstrate that the antigens in healthy intestinal microflora are sufficient for the induction of immune responses that lead to IBD-like disease.

Disruption of T-cell activation

CD4+CD45RB^{Hi} T-cell transfer colitis

The CD4+CD45RB^{Hi} T-cell transfer-induced IBD model to immunodeficient mice uses fluorescent activated cell sorter to remove the regulatory T-cell population from the transferred naïve T-cell population (which has potential effector function). Disease develops spontaneously 6 to 8 weeks after transfer into syngeneic immunodeficient mice. The regulatory CD4+CD45RB^{Lo} T-cells, when transferred alone, do not cause disease, indicating that the model is not a form of graft-versus-host disease. Rather, these T-cells can actually prevent the disease caused by CD4+CD45RB^{Hi} T-cells in a numerically disproportionate manner. The primary pathology is in the colon and there is attenuated disease when the level of intestinal flora is reduced in mice housed in a gnotobiotic environment [44••]. Osteopenia has also been observed in this model, and the model has been successfully used to study anti-bone resorptive agents that may have utility in treating IBD-associated bone loss [45]. The regulatory T-cell population comprises CD25+ cells, and mediates anti-inflammatory effects via IL-10, transforming growth factor-β (TGFβ) and T-lymphocyte-associated antigen (CTLA)-4. This regulatory T-cell population can reverse established disease as well as prevent disease development caused by the effector cells [46,47]. There have been a number of benchmarking studies with drugs demonstrating efficacy in this model with recombinant CTLA-4-Fc, as well as with antagonists of TNFα, OX40 ligand and IFNγ [48,49•,50,51]. Many of these agents are now being tested for treatment of IBD in the clinic, including fontolizumab, the antibody to IFNγ from Protein Design Laboratories Inc, and the recombinant form of CTLA-4-Fc (abatacept), which is currently being developed by Bristol Myers Squibb Co Ltd. Administration of epithelial repair agents such as keratinocyte growth factor are also effective, demonstrating that intervention in more downstream events can also be of therapeutic benefit [24]; however, the model exhibits significant variation across different laboratory facilities, likely due to variable intestinal microflora, which is a difficult parameter to characterize and manipulate.

T-cell receptor deficiency colitis

Several IBD studies have been conducted in T-cell-deficient mice. T-cell receptor (TCR)α chain knockout mice develop more severe colitic disease than TCRβ chain knockout mice and, importantly, TCRγδ knockout mice develop no disease [52]. Antagonism studies in TCRα knockout mice have demonstrated that IL-4 is the major effector cytokine, and, thus, these models are viewed as being more representative of Th2-like autoimmune disease, indeed, histologically, they are more representative of human UC. B-cells have not been demonstrated to play a major role in the pathogenesis of this type of IBD. The exact mechanism leading to intestinal inflammation in this model is, however, unclear, and this model has not been used routinely for preclinical testing of therapeutics [53,54].

Other T-cell disruption models of colitis

STAT4 transgenic mice exhibit an exaggerated Th1-type response due to excessive responsiveness to IL-12 signaling, and STAT4 is a probable transcription factor for IFNγ, which is consistent with a Th1-type phenotype [55,56]. There is still a need for gnotobiotic and further benchmarking studies in this model. Recently, T-bet transgenic mice have been described in which overexpression of the T-box protein induces a colitic phenotype and renders mice hyper-responsive to IFNγ and unresponsive to IL-4; this is a classic

demonstration of inflammation due to Th1 polarization, although it is not yet clear whether this is a true immune response against intestinal microflora [57•]. An IL-12-driven Th1-type colitic disease also occurs in CD3ε TG26 mice, but this model has not been extensively benchmarked [56,58]. Another interesting model is the Gαi2 knockout mouse, which develops colitic disease. This mouse harbors an unusual defect in an intracellular signaling molecule, resulting in the over-production of IL-12 and TNFα [59]. An IBD-like phenotype has also been ascribed to CTLA-4 knockout mice. Although the absence of this molecule does cause severe autoimmune disease, it likely reflects a more systemic inflammatory response rather than provide a true reflection of IBD-like disease, because the inflammation is not more prominent in intestinal tissue relative to other organs [60]; however, given the pivotal role of the B7/CTLA-4 co-stimulatory pathway in T-cell activation and the reported efficacy of CTLA-4-Fc in mouse models of IBD, the recombinant CTLA-4-Fc molecule has strong conceptual appeal for the treatment of IBD [50].

These T-cell perturbation models clearly reveal a primary role for T-cells in the induction and maintenance of IBD. It seems clear that a threshold for T-cell activation exists and that a delicate balance between effector T-cells and regulatory T-cells defines when disease occurs: this paradigm is better investigated experimentally in mice but is being established experimentally in humans [61,62].

Disruption of cytokine synthesis/regulation

IL-10 deficiency colitis

The IBD-like disease that occurs in IL-10 knockout mice is notable for the appearance of both small intestine and colonic disease, and the inflammation is attenuated in a germ-free environment [63,64]. The phenotype of the CRF2-4 subunit knockout of the IL-10 receptor (via disruption of *CRFB4*, the gene encoding CRF2-4) confirms the functional inactivation of the IL-10 pathway as a trigger for IBD-like disease [65]. The phenotype of IL-10-deficient mice has been hypothesized to be due to an inability to downregulate the B7.1 and B7.2 co-stimulatory molecules, or due to a lack of TGFβ response further downstream, although neither hypothesis has been clearly established experimentally. The IBD-like disease in IL-10 knockout mice has prompted the testing of recombinant human IL-10 in human trials but no efficacy was observed in controlled phase III clinical studies [66]. However, more recent studies in mouse models of IBD have demonstrated clear efficacy with targeted delivery of IL-10 to the gut via a transgenic or microbiological vector, raising the possibility that systemically administered IL-10 does not achieve sufficient local exposure to attenuate human IBD [67,68]. Early intervention of IBD via IL-12 and TNFα antagonism has been effective in this model, indicating a Th1-type pathology [64,69,70••]. Osteopenia has also been described in these mice [71]. Similarly to other spontaneous immunologically mediated models of IBD, there is variation in penetrance and severity depending on the laboratory facility, presenting significant but addressable difficulties for the controlled preclinical testing of therapeutic agents.

TNFα overexpression colitis

Deletion of AU-rich elements in the 3' untranslated region of the TNFα gene leads to TNFα overexpression. Mice with this deletion, known as $TNF^{\Delta ARE}$ mice, develop both arthritis- and IBD-like disease [72]. Consistent with observations that TNFα antagonists exhibit efficacy in CD and UC, the model implicates TNFα as a primary driver of disease. The model has also been useful for revealing the cross-talk between different cytokine systems such as IL-10 and TNFα [72]. Further studies on the roles played by the different TNF receptor molecules will also be possible using this and other TNFα-dependent models [73].

Other cytokine disruption models of colitis

An IBD-like phenotype in IL-7 transgenic mice has been described [74]. IL-7 is a key growth and differentiation factor for epithelial cells as well as intra-epithelial and lamina propria lymphocytes. Excess IL-7 activates lymphocytes and ultimately causes them to apoptose [74]. IL-7 can also exacerbate disease in other mouse models of IBD [75]. Colitis occurs early in life for IL-7 transgenic mice, and in the chronic phase bears similarities to human UC; changes in IL-7 levels have also been noted in human disease [76].

Several variations of targeted disruption of the murine IL-2 pathway have been created and some are associated with an IBD phenotype. IL-2 knockout mice (as well as IL-2Rα and IL-2Rβ, but not IL-2Rγ knockout mice) develop colitic disease. In the IL-2 knockout model, gastrointestinal disease is attenuated in a germ-free environment, but the mice also exhibit a general lymphoid hyperplasia and, as IL-2 is a critical factor for all T-cell development, the relevance of this model to human IBD is perceived as being somewhat limited [77,78,79••,80].

An IBD-like phenotype has also been described in TGFβ knockout mice. Similarly to CTLA-4 knockout mice, the inflammation is more systemic in nature and is not more prominent in intestinal tissue relative to other organs [60]; however, targeted disruption via TGFβ dominant negative receptors in the T-cell or epithelial cell can limit the disease, leaving inflammation in the colon or lung only [81••,82,83].

Other cytokine targets that will likely be tested by antagonism in the clinic include IL-18, which has been well validated as a target in mouse models of IBD [26,84-86], and IL-6, which is already being studied with tocilizumab, an antibody to the IL-6 receptor in several inflammatory diseases [87]. More newly discovered cytokines such as IL-23 and IL-27 (which are closely related to IL-12 but can also act independently), as well as TNF-like cytokine TL1A, provide intriguing possible new drug targets, although more basic biological studies are needed before these concepts can be tested in humans [88-90]. There is strong evidence from human genetic and serum associative studies that imbalances in the IL-1/IL-1 receptor antagonist system play a role in human IBD, although no definitive clinical trial for IBD with an IL-1 antagonist has yet been performed [91-93].

These cytokine perturbation models clearly demonstrate that different targeted disruptions can ultimately converge upon a final, common phenotype.

Other spontaneous models of IBD

The spontaneous intestinal disease that occurs in C3H/HeJBir mice has been known for some time. These mice lack toll-like receptor (TLR)4 and hence are unresponsive to stimulation with lipopolysaccharide, but they do recognize a select number of enterically derived bacterial antigens [94]. The disease has been characterized as a Th1-driven phenotype, and T-cells from these mice stimulated by bacterial lysates can transfer disease to severe combined immunodeficiency mice, confirming that specific mucosal microflora antigens can trigger and mediate IBD-like disease [95,96].

One of the most interesting developments of recent years has been the description of the phenotype of SAMP1/Yit mice. These AKR mice have been extensively inbred to establish accelerated senescence, but they also develop a discontiguous ileitis that is histologically similar to human CD [97,98••]. This is noteworthy as most other mouse models of IBD develop gross, diffuse inflammation of the colon and there is a scarcity of models that recapitulate inflammation of the small intestine, particularly the discontiguous 'skip' lesions associated with human CD. Experimentally, this has been demonstrated to be a transferable Th1-type response to intestinal microflora, and the disease is attenuated by antibiotics, probiotic bacteria and TNFα and IFNγ antagonism [99-102]. Furthermore, fistulizing disease has been reported for this model, which is intriguing and represents a significant breakthrough in recapitulating the clinical features of at least the CD variant of human IBD [101]. Many putative anti-inflammatory compounds are being tested in this model and will likely generate interesting and useful data.

Emerging therapeutic options

A schematic for the pathogenesis of IBD with potential therapeutic interventions listed for the various stages of the pathway is provided in Figure 2. There has been a recent focus on treating IBD via the interruption of cell trafficking. Natalizumab (Tysabri; Biogen Idec Inc/Elan Corp) is an antibody specific for the α4 integrin subunit expressed primarily on T-cells, and has shown promise in the treatment of multiple sclerosis and CD [103,104]; however, the development of progressive multifocal leukoencephalopathy in a small number of patients administered the drug has led to its voluntary suspension [105]. MLN-02 (Millennium Pharmaceuticals Inc), an antibody to the α4β7 integrin, binds a less ubiquitously expressed integrin heterodimer expressed on T-cells trafficking to the gut [106•]. As well as targeting the integrins expressed on trafficking cells, the chemokines that attract immune cells to the inflamed gastrointestinal tract are also targets for therapeutic intervention. Traficet-EN (ChemoCentryx Inc) is a small-molecule antagonist of the CCR9 chemokine receptor that recruits CCL25-bearing lymphocytes to the gastrointestinal tract. This drug is currently in phase II clinical trials for the treatment of CD and represents a novel, targeted small-molecule approach that is expected to should yield interesting data [107-110].

Intracellular targets are also receiving increasing attention. A p38 mitogen-activated protein kinase blocker, semapimod (Cytokine PharmaSciences Inc), has provided some promising clinical data, but its efficacy is so far unproven under rigorous clinical trial conditions [111]. Thalidomide and its newer analogs from CelGene Corp are also being developed as potential therapies for IBD [112-114].

New paradigms in the treatment of IBD continue to emerge. One example is the use of a stimulatory cytokine such as sargramostim (Berlex Laboratories Inc/Immunex Corp). Sargramostim has been studied in phase II clinical trials and the resulting data appear to support its efficacy for treating CD [115••,116]. The mechanism of action of sargramostin is unclear, but it may be related to its ability to increase the elimination of microorganisms, or to downregulate a Th1-type phenotype or to stimulate the expansion of plasmacytoid dendritic cells [117].

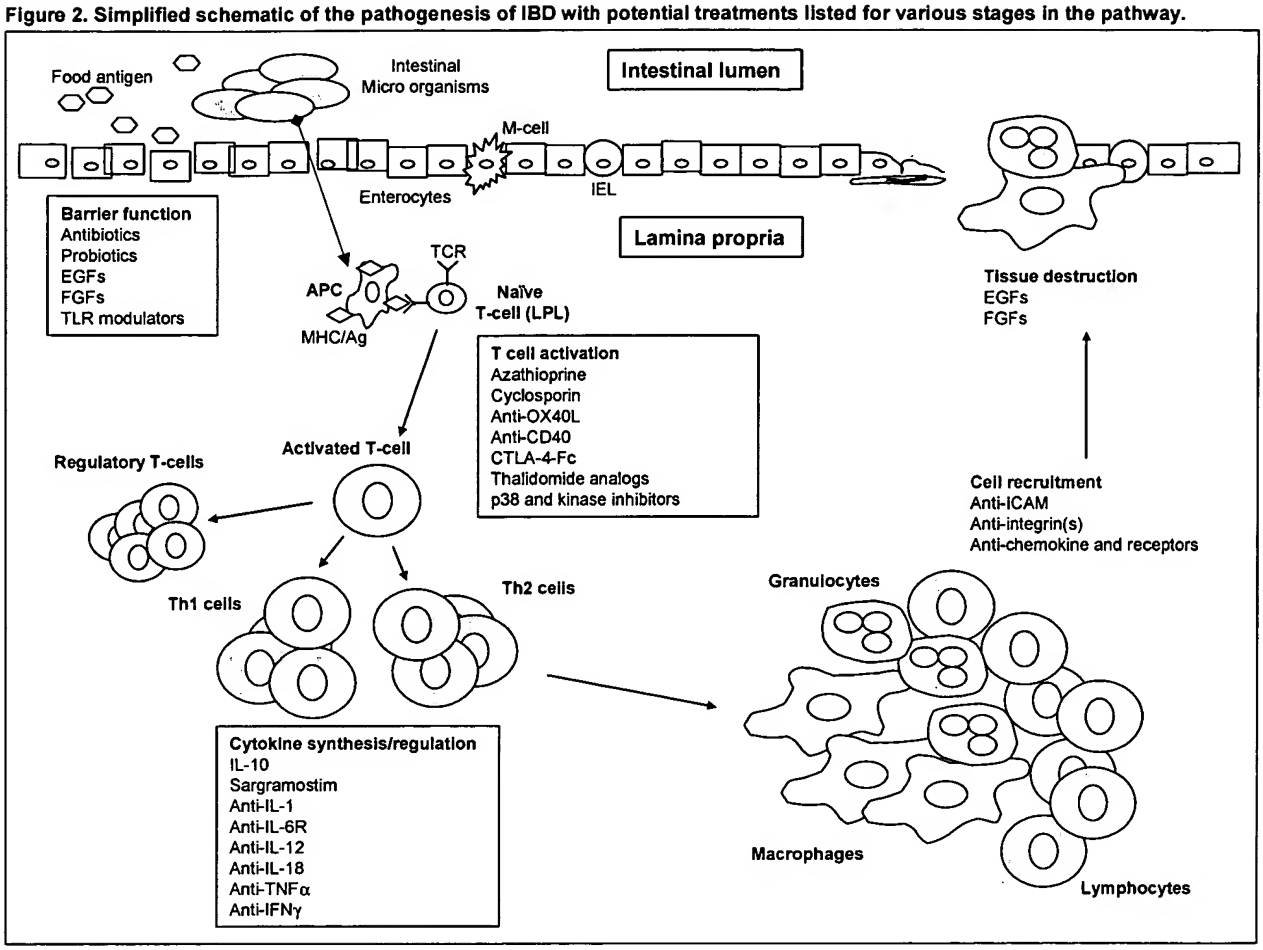
Modulation of the putative disease-initiating antigens using antibiotics, or, more recently, probiotics, also offers promise for the effective therapy of IBD. Antibiotic therapy has been used to treat IBD for some time with varying degrees of success, likely due to the complexity of the intestinal microflora and their variation over time and between individuals [118,119]. The exact identity of the triggering microorganism(s) in IBD pathogenesis is still unknown but the recently described *Pseudomonas* spp I2 antigen is a strong candidate [120•]. The use of probiotics (ie, defined, live microbiological supplements) has demonstrated potential in several mouse models of IBD, and clinical trials are ongoing [121,122]. These probiotic microorganisms may function by eliminating or out-competing the triggering microbial antigen in immunopathogenesis and/or by directly modulating the mucosal immune system [123-125].

Finally, new paradigms are also emerging with regard to the therapeutic modalities being used. There have been several preclinical and clinical studies with antisense therapeutics to intercellular adhesion molecule (ICAM) [126,127], and other molecules are being targeted by this approach [128]. These therapeutics have proved clinically ineffective in IBD treatment so far [129], but it is unclear whether this result is related to the target or to the modality. There is currently one antisense drug (fomivirsen from ISIS Pharmaceuticals Inc) approved for the treatment of AIDS-related cytomegalovirus retinitis and the associated modality is likely to be studied further in the future.

Bench to bedside and back to bench

The use of experimental mouse models to mimic human IBD has generated a wealth of interesting scientific data, especially over the past decade; however, the ultimate test for any proposed therapeutic is in the clinic. Uncontrolled open-label studies in humans are a logical first step, however, the variable natural course of human IBD and the high rate of response to placebo necessitates a controlled double-blind study, with dozens of patients in each arm, before any definitive conclusions about the efficacy of a new drug can be drawn.

Figure 2. Simplified schematic of the pathogenesis of IBD with potential treatments listed for various stages in the pathway.



APC Antigen-presenting cell, **EGF** epidermal growth factor, **FGF** fibroblast growth factor, **ICAM** intercellular adhesion molecule, **IEL** intra-epithelial lymphocyte, **IFN** interferon, **IL** interleukin, **LPL** lamina propria lymphocyte, **MHC/Ag** major histocompatibility complex antigen, **TCR** T-cell receptor, **TLR** toll-like receptor, **TNF** tumor necrosis factor.

Given the limitations of preclinical testing only a few of the agents that progress to human clinical trials are likely to be successful, but when success occurs the benefits for patients can be dramatic. There are now several examples of TNFα antagonists being used successfully in treating human inflammatory diseases such as rheumatoid arthritis and psoriasis, but in the case of IBD it is clear that not all TNFα antagonists are equal. Infliximab (from Centocor Inc), a monoclonal antibody to human TNFα, has proved a highly successful therapy for many, but not all, CD patients, whereas the recombinant soluble TNFα receptor etanercept (from Amgen Inc/Wyeth Research) has not proved successful for this indication, despite both drugs having clear efficacy in human rheumatoid arthritis. The reason for this disparate result is postulated to be due to the ability of infliximab to act as a cell-depleting agent, eliminating cells that bear membrane-bound TNFα [130,131]. Why this might be important in treating IBD relative to arthritis is unclear, and further studies of both agents will likely prove revealing.

The description of the nucleotide-binding oligomerization domain 2 (NOD2; encoded by the *CARD15* gene) mutation as a factor contributing to susceptibility in human CD is a clear validation of the success of human genetic studies. The intracellular NOD2 molecule is hypothesized to be involved in the development of the immune response to microbial antigens, but it is neither a necessary nor a sufficient requirement for CD as only 20% of CD patients have a NOD2 defect [132••]. NOD2 knockout and mutant mice have been generated and these exhibit increased susceptibility to induced IBD, increased TLR2-mediated activation of nuclear factor κB-c-Rel and an enhancement of Th1-type responses [133-136].

Conclusion

From a targeted drug development perspective it is more useful to consider models on the basis of phenotype, rather than an imposed genotype which is unlikely to represent an underlying genetic lesion in human IBD. There are many animal model options to choose from for IBD and so the

appropriateness of a model system must be considered in the context of the proposed mechanism of action of the potential therapeutic. One must also consider the logistical ease of use of the model (eg, penetrance, time to disease, synchronicity of progression and reproducibility) and the species-specificity of the reagent. There are some obvious current limitations of disease models in the drug development effort. The two most notable are: (i) the lack of a useful system to predict immunogenicity of biologicals; and (ii) the lack of a system to predict the effects of ongoing immunosuppression with any particular immuno-modulatory drug. As always, the ultimate experimental data will need to be generated in humans; however, there is no doubt that the significant efforts made over the past few years by many researchers in the area of animal models of IBD has yielded valuable scientific data, which has generated significant benefit for CD and UC patients.

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•• of outstanding interest
• of special interest

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